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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 04/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,682	BJERKVIG, ROLF	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communicati n appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14-21,24-28,30 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14-21,24-28,30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on1/22/03, as Paper No. 12. The amendment has been entered. Claims 12, 17, 19, 21 and 32 have been amended. Claims 13, 22, 29 and 31 have been cancelled. No new claims have been added. Claims 12, 14-21, 24-28, 30 and 32 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 1-22-03 has been considered. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The phrase "substantially free of endotoxin" in claim 20 is a relative term which renders the claim indefinite. The phrase "substantially free of endotoxin" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without a clear definition of the phrase "substantially free of endotoxin", one of ordinary skill in the art would not reasonably be able to determine the metes and bounds of the claim (i.e. what degree or toxin-free would be considered "substantially free of toxin"). Therefore, the claim is indefinite.

8. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claim is drawn to a method for producing the composition of claim 12, comprising the step of encapsulating a producer cell in a one-step procedure. However, the claim does not set forth what the one-step procedure comprises. Therefore, the actual method step is omitted from the claim.

9. Furthermore, because the method of claim 24 is incomplete (i.e. missing essential method steps). One of ordinary skill in the art would know how to make/use the method of claim 24. Therefore, claim 24 is also rejected under 35 USC 112, first paragraph as well.

10. Claims 27, 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for treating a mammalian patient afflicted with a CNS tumor (or brain tumor) comprising the step of directly administrating to the CNS tumor (or brain tumor) an effective amount of the pharmaceutical composition of claim 26; so as to inhibit the growth of said tumor JKA 4/7/03 does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method of treating cancer by administering an encapsulated producer cell which produces an effective amount of a therapeutic polypeptide. Therefore the nature of the Invention is cancer therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims encompass administering the pharmaceutical composition to any part of the body for treating a CNS tumor including a brain tumor.

The unpredictability of the art and the state of the prior art

As mentioned in the previous Office Actions, there are several problems associated with using encapsulated cells as therapeutic compositions. In particular, it is noted that the prior art (Vista) teaches, "despite promising results reported in several animal experiments, limited graft survival may occur. This is attributed to host immune reactions against the implant" (see p.204 under Biocompatibility); "microcapsule graft failure is often associated with fibrotic outgrowth of the capsules" (see p. 205, first paragraph); "several cases report that the host produces immunoglobulins against the encapsulated material as well as the secreted recombinant proteins" (see p. 205, under Reaction of the Recipient Against the Encapsulated Cells). Therefore, the prior art teaches that there are number of different problems, in particular with respect to the immune response against the implanted material and the therapeutic polypeptide produced by the implant. Although Applicants note in their response that the immune response in the CNS would be much less than in non-CNS tissue, the claims are not limited to directly administering the pharmaceutical composition to the site of the CNS having the tumor. In fact, as mentioned above, the claim encompasses administering the composition to any part of the body to treat a CNS tumor. Administering the composition to any tissue other than CNS-tissue would likely result in an immune response as indicated in the prior art. Furthermore, one of ordinary skill in the art would not be able to reasonably expect that administration of the pharmaceutical composition to a site other than the site of the CNS tumor would be effective because of the reasons above, and additionally because there could not be a reasonable expectation for the encapsulated cell to travel to the site of the tumor, or for the therapeutic polypeptide produced by

the encapsulated cell to travel to site of the tumor considering the defense mechanisms of the host, including the immune response, and the blood/brain barrier.

Working Examples and Guidance in the Specification

The specification has only one in vivo working example. The example encompasses treatment of a CNS tumor comprising administering (by implanting into the tumor region of the brain) an encapsulated cell which expresses endostatin. The specification does not provide teachings sufficient to overcome doubts raised in the art with regards to methods of treatment by administering the therapeutic composition to any place other than directly to the site of the CNS tumor. It is not predictable that the broadly claimed treatment method would effectively achieve any therapeutic benefit when the composition was administered to any place other than the site of the CNS tumor.

Quantity of Experimentation

The quantity of experimentation required for one of ordinary skill in the art to be able to practice the claimed method with a reasonable expectation of success is deemed to be undue, as one of ordinary skill in the art would have to be able to overcome the teachings indicated in the prior art (and mentioned above) in order to administer the pharmaceutical composition to a site other then a CNS-tumor site and reasonably expect the composition to treat the tumor.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of recognized in the art, the breadth of the claims, the limited working examples and guidance in the specification; and the high degree

of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Claim Rejections - 35 USC § 103

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 12, 14-21, 24-28, 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebischer (WO 97/38707 A1, 1997) in view of O'Reilly (US Patent 5,854,205, filed 10-22/1996) and further in view of Skjak-Braek (U.S. Patent 5,459,054; 1995).

Aebischer teaches composition comprising a producer cell that expresses a molecule (here FasL) that can be used as a treatment to inhibit CNS tumor growth (see p. 2-3) wherein the cell is encapsulated to protect the cell from the host's immune response (see p. 14).

Aebischer does not teach that the molecule is endostatin.

Aebischer does not teach that the encapsulating matrix is made up of immunoisolating alginate having a G content of above 15%, that the therapeutic molecule affects tumor neovascularization, that the producer cell is present in a bead or a microbead, or the therapeutic molecule produced by the encapsulated cell is endostatin.

O'Reilly (US Patent) teaches that endostatin is a polypeptide which can inhibit cell proliferation and angiogenesis (see abstract). O'Reilly teaches that nucleic acid encoding endostatin can be used to modulate endothelial processes in vivo and to treat disease by gene therapy (see column 9, lines 29-45). O'Reilly indicates that nucleic acid sequence corresponding to the amino acid sequence could be prepared by one of ordinary skill in the art based upon the

amino acid sequence (see column 9, lines 39-45). O'Reilly teaches that endostatin protein and the nucleic acid encoding endostatin can be used to treat a number of different diseases, including solid tumors (see column 4, lines 4-19), and specifically tumor metastases, including acoustic neuromas, neurofibromas, etc. (see column 10, lines 33-60) which includes tumors of the CNS and brain.

Skjak-Braek et al. teaches a composition comprising a producer cell which does not express a molecule that inhibits tumor growth, but is an encapsulated cell wherein the producer cell is encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, above 50%, 60-80%, and 80-100%, wherein the producer cell is encapsulated in a bead, wherein the alginate is substantially pure of endotoxin, (see abstract; col. 4, lines 44-67; col. 7, lines 15-18; and Example 7). Skjak-Braek et al. also teaches that the encapsulated cells are living cells (col. 4, lines 7-11) which are naturally occurring or genetically engineered prokaryotic or eukaryotic cells (see col. 4, lines 53-57), and that the encapsulated cells "can be implanted or transplanted in vivo into mammals without inducing any substantial immunogenic reaction or fibroblast formation" and can be used "as a drug or biological material delivery system." (See col. 4 lines 44-58).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Aebischer such that 1) the cell expresses endostatin and 2) the immunoisolating alginate taught by Skjak-Braek is substituted for the encapsulating matrix of Aebischer, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to create an encapsulated producer cell for treatment of a brain/CNS tumor by substituting the nucleic acid encoding

endostatin for the nucleic acid encoding FasL in the producer cell, because 1) both molecules were known in the art as cancer therapeutic molecules, and 2) specifically, because O'Reilly teaches that the nucleic acid encoding endostatin could be used to treat solid tumors and tumor metastases including acoustic neuromas, neurofibromas. Furthermore, one of ordinary skill in the art would have been motivated to encapsulate the producer cell indicated above (in view of Aebischer and O'Reilly) with the immunostimulating alginate taught by Skjak-Braek because Sjak-Braek teaches that the alginate with a high concentration of G and low concentration of M has a reduced immunostimulatory effect when transplanted into a mammal, which protects the cell from the mammal's immune response and fibroblast formation better than an alginate with a high concentration of M and a low concentration of G (such as in Aebischer) (see columns 1-3 and column 4, lines 44-66; column 6, lines 33-54).

Response to Arguments

2. Applicant's arguments filed 1-22-03 have been fully considered but they are not persuasive.

Regarding the rejection of claims under 35 USC 112, first paragraph, Applicants argue that the claims are enabled because the instant invention encompasses implantation of the therapeutic composition to the CNS/brain and that there would be a reduced immune response/fibroblast infiltration in the CNS/brain.

In response, it is respectfully pointed out that the claims are not limited to directly implanting the therapeutic composition in the CNS/brain of a mammal, and in fact encompass

administering the composition to any part of the animal to treat a CNS/brain tumor. Because of the breadth of the claim and for the reasons set forth above, the claims are not enabled for the full scope encompassed by the claims.

Regarding the rejection of claims under 35 USC 103, Applicants argue that the references do not teach every element of the invention, that there is no motivation to combine the references (except using the hindsight reasoning in view of the specification). Applicants also specifically argue that there is no teaching that endostatin could be used to treat a CNS/brain tumor.

In response, that Applicants arguments regarding the lack of a teaching that endostatin could be used as a therapeutic agent to treat a CNS/brain tumor is persuasive to withdraw the previous rejection. However, a new rejection has been set forth using a reference which specifically teaches that endostatin (and a nucleic acid encoding it) could be used to treat a CNS/brain tumor.

The response to Applicants arguments as they pertain to the new reject is below.

3. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

4. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the references is suggested by O'Reilly and Skjak-Braek. First O'Reilly teaches that endostatin can be used to treat CNS/brain tumors. Second Skjak-Braek teaches that encapsulating a therapeutic cell with an alginate comprising high-levels of G and low levels of M results in a reduced immune response compared to other alginates. Therefore one of ordinary skill in the art would have been motivated to make the claimed invention with a reasonable expectation of success.

Regarding Applicants arguments that the rejection did not address the composition where angiostatin, thrombspondin, or prolactin are the therapeutic molecules. It is respectfully pointed out that the claims encompass a Markush group of therapeutic molecules and rejection of one of the members of the Markush group (here, endostatin) is sufficient to reject the claims.

The rejection of claims under 35 USC 112, first paragraph (written description) has been withdrawn in view of the amendment.

The rejection of claims under 35 USC 112, second paragraph (indefiniteness) has been withdrawn in view of the amendment. However, a new rejection has been set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
April 7, 2003

DAVE T. NGUYEN
PRIMARY EXAMINER